Title: Primary and metastatic brain cancer genomics and emerging biomarkers for immunomodulatory cancer treatment

Authors: F. Passiglia, C. Caglevic, E. Giovannetti, JA. Pinto, P. Manca, S. Taverna, A. Listì, I. Gil-Bazo, LE. Raez, A. Russo, C. Rolfo

PII: S1044-579X(17)30218-3
DOI: https://doi.org/10.1016/j.semcancer.2018.01.015
Reference: YSCBI 1446

To appear in: *Seminars in Cancer Biology*

Received date: 17-11-2017
Revised date: 24-1-2018
Accepted date: 25-1-2018

Please cite this article as: Passiglia F, Caglevic C, Giovannetti E, Pinto JA, Manca P, Taverna S, Listì A, Gil-Bazo I, Raez LE, Russo A, Rolfo C.Primary and metastatic brain cancer genomics and emerging biomarkers for immunomodulatory cancer treatment.*Seminars in Cancer Biology* https://doi.org/10.1016/j.semcancer.2018.01.015

<AT>Primary and metastatic brain cancer genomics and emerging biomarkers for immunomodulatory cancer treatment. , , F. Passiglia[1*], C. Caglevic[2*], E. Giovannetti[3], JA. Pinto[4], P. Manca[5], S. Taverna[1], A. Listì[1], I. Gil-Bazo[6], LE. Raez[7], A. Russo[1], C. Rolfo[8#<AU>]
##Email##christian.rolfo@uza.be##/Email##
<AFF>[1]Department of Surgical, Oncological and Stomatological Disciplines, University of Palermo, Italy
<AFF>[2]Unit of Investigational Cancer Drugs, Instituto Oncologico Fundación Arturo López Pérez, Santiago, Chile
<AFF>[3]Department Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands
<AFF>[4]Unit of Basic and Translational Research, Oncosalud-AUNA, Lima, Peru
<AFF>[5]Medical Oncology Department, Campus Biomedico, University of Rome, Rome, Italy
<AFF>[6]Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain
<AFF>[7].Thoracic Oncology Program, Memorial Cancer Institute, Memorial Health Care System, Florida International University, Miami, FL, USA
<AFF>[8]Phase I-Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital (UZA) and Center for Oncological Research (CORE) Antwerp University, Edegem, Antwerp, Belgium

*both authors contributed equally
<PA>[#]**Corresponding author: Prof. Christian Rolfo,** MD, PhD, Phase I -Early Clinical Trials Unit Director, Oncology Department, University Hospital Antwerp UZA, Wilrijkstraat 10, 2650 Edegem. Belgium, Tel.: +32 3 821 36 46.

<ABS-HEAD>Abstract

<ABS-P>Recent studies with immunomodulatory agents targeting both cytotoxic T-lymphocyte protein 4 (CTLA4) and programmed cell death 1 (PD1)/ programmed cell death ligand 1 (PDL1) have shown to be very effective in several cancers revealing an unexpected great activity in patients with both primary and metastatic brain tumors. Combining anti-CTLA4 and anti-PD1 agents as upfront systemic therapy has revealed to further increase the clinical benefit observed with single agent, even at cost of higher toxicity. Since the brain is an immunological specialized area it‘s crucial to establish the specific composition of the brain tumors’ microenvironment in order to predict the potential activity of immunomodulatory agents. This review briefly summarizes the basis of the brain immunogenicity, providing the most updated clinical evidences in terms of immune-checkpoint inhibitors efficacy and toxicity in both primary and metastatic brain tumors with the final aim of defining potential biomarkers for immunomodulatory cancer treatment.
<KWD>Keywords: Brain; metastasis; immunotherapy; CTLA4; PD1/PDL1; biomarkers

<H1>1. Introduction

Primary malignant brain tumors and central nervous system (CNS) metastasis are associated with poor prognosis. Despite multimodality approaches, including local surgical and radiation treatments and systemic chemotherapies, morbidity and mortality remain still very high, reaching a median overall survival (OS) of about 12 months. The natural history of these patients is characterized by a progressive neurological deterioration and a rapid decline of their quality of life (QoL) because of the very aggressive pattern of growth associated with these tumors and the toxicity profile related to the combination therapies. Thus, we have an urgent clinical need of new effective treatment strategies which are able to extend the survival of patients affected by both primary and metastatic brain cancers preserving their QoL.
There are now several new biological drugs available that are effective for brain metastasis, like the third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) osimertinib in lung cancer. This compound is able to selectively target both the EGFR activating and resistant